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THE MEDICINAL PROPERTIES OF PHYTOCHEMICALS IN CATHARANTHUS ROSEUS - A REVIEW

Renjini K. R., Gopakumar G. and Latha M. S.*

Department of Chemistry, Sree Narayana College, Chengannur, Kerala, India.

***Corresponding Author: Latha M. S.**

Department of Chemistry, Sree Narayana College, Chengannur, Kerala, India.

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ABSTRACT

Plants have been a rich source of compoundsfor the development of clinically useful therapeutic agents. *Catharanthus Roseus*, also known as Madagascar Periwinkle is a pretty ornamental plant of Apocyanate family. Medicinal value of this plant has been known from ancient Mesopotamian age. The plant contains enormous phytoconstituents which are used intraditional Indian system of Ayurvedic medicine and conventional Chinese medication and other curative systems. All parts of the plantare reported to contain alkaloids. More than400 unique alkaloids had been isolated and named from this plant. Its curative action is due to the presence of alkaloids like Ajamalicine, serpentine and reserpine which are known for hypotensive, anti-diabetic, anti-microbial, anti-oxidantand antispasmodic properties. With the presence of cancer fighter Vincaalkaloids vincristine, vinblastine, vinorelbine and vindesine, it became eminent anticancer herb along with many other therapeutic effects. Vincristine is in the List of Essential Medicines of World Health Organization's, the most important medication needed in a basic health system. This review gives an overview of the medicinal properties of the phytochemicals present in *Catharanthus Roseus*.

KEYWORDS: *Catharanthus Roseus*; Phytochemicals; Vinca Alkaloids; Anticancer; Vincristine; Vinblastine.

INTRODUCTION

The growing demand for novel drugs that can overcome the problem of drug resistance contribute to a revival of interest in plant based compounds for drug discovery. Nature hasgiven manymedicinal plants for our health andsurvival.[1] A great part of herbalcomposites are used as main particle in drug discovery to produce synthetic molecular analog. This indicates the significance of study of phytochemicals in diversity oriented synthesis (DOS) of natural product-like pharmacompounds.[2] *Catharanthusroseus* is very common in Madagascar -an indian ocean island plant which is one of the few pharmacological plants that have a quite long history.[3] It plays considerable role in herbal and traditional medicine for treatment of various diseases like diabetes, hypertension, asthma, constipation, cancer, depression, muscle pain, bleeding gums, mouth ulcers, sore throats, cystitis, menstrualproblems, gastritis, enteritis, diarrhea, urogenital infection, menorrhagia, rheumatism, stomach ache and skin problems like dermatitis, eczema and acne.[4,5] Based on the flower color there are two major cultivarsin C.roseus. One is pink flowered "Rosea" and another white colored "Alba".[6] Over the past two decades there are more than 100 varieties are developed though breeding technique. They have not only improved floral traits but also it is tolerant to disease and have boosted herbage and alkaloid yield.[7]

Figure 1. Madagascar periwinkle-Rosea.

Figure 2. Madagascar periwinkle –Alba.

Morphology

C.roseus is an annual evergreen sub herb or herbaceous plant growing to 1 m. tall and secretes milky latex.[8] The roots extend to 70 cm. in depth. Stems are cylindrical (terete), longitudinally ridged or narrowly winged, green or dark red, pubescent at least when young. The leaves are oval to oblong, 2.5- 9.0 cm. long and 1- 3.5 cm. broad, glossy green above and pale green below with a pale midrib and a short petiole about 1- 1.8 cm. long. They are arranged in the opposite pairs. The flowers arepentamerous, actinomorphic and white to dark pink with a dark red center, with a basal tube about 2.5- 3 cm. long and a corolla about 2-5 cm. diameter with five petal like lobes.[9] The fruit is a pair of follicles about 2-4 cm. long and 3 mm broad, with numerous black seeds.[10]

Classification

Domain: Eukarya: eukaryotes.
Kingdom: Plantae: plants.
Subkingdom: Tracheobionta: vascular plants.
Superdivision: Spermatophyta: seed plants.
Division: Magnoliophyta: flowering plants.
Class: Magnoliopsida: dicotyledons.
Subclass: Asteridae.
Superorder: Gentiananae.
Order: Gentianales.
Family: Apocynaceae: dogbane.
Subfamily: Rauvolfioideae.
Tribe: Vinceae.
Genus: Catharanthus G. Don.
Specific epithet: Roseus (Linnaeus) G. Don.[11-14]

Geographical Distribution

The plant is distributed all through subtropical Asia, Africa and also in America and has been utilized both for decoration and medicine. All parts of the plant are useful including the roots, leaves, flowers and stems. It prefers well drained sandy loams soil and moisture with excellent soil drainage.[15] It can be propagated by Cuttings and seeds and it has tolerance of cooler growing condition in temperate regions.

Table 1. Folkloric Uses of *CatharanthusRoseus* and its vernacular names in different countries.

Country(Vernacular name)	Uses
Philippines (Tsitsirika)	Decoction of leaves used in diabetes & stomach cramps. Root decoction for intestinal parasitism; as emmenagogue; may produce abortion. Infusion of leaves used for treating menorrhagia. Crude leaf extract has anticancer activity. Recent use of roots for anticancer applications. Roots used for dysentery.[16]
Madagascar	The bitter and astringent leaves used as vomitive; roots used as purgative, vermifuge, depurative, hemostatic and toothache remedy.
Mauritius	Infusion of leaves used for indigestion and dyspepsia.
India, West Indies, Nigeria & Jamaica(Kanniedood)	Used for diabetes.
Cuba and Jamaica	Flower extract used for eyewash in infants
Bahamas	Flower decoction used for asthma.
Malaysia(KemuntingCina)	Plant decoction used for diabetes, hypertension, insomnia and cancer.
China (Yan laihong, Riricao, Ririxin, San wan hua, Zhang chunhua).[17]	Used for dysmenorrhea, diabetes & malaria.
India(Sadabahar, Baramassi, Ainskati, Ushamanjairi).[18]	Juice of leaves used for bee stings.

Phytochemical Components

Phytoconstituents present in *C.roseus* mainly include carbohydrates, alkaloids, glycosides, flavonoids, tannin, saponins, proteins, amino acids, fats and oils.[19] This plant produces more than 100 monoterpenoidindole alkaloids (TIA) in different organs.[20] Among this principal component is vindoline(up to 0.5%). Other compounds arevincaleukoblastine (vinblastine), 22-oxovincaleukoblastine (vineristine), reserpine, vincamine, alstonine, leurocristine, ajmalicine, vinine,

vinomine, vinoxine, vintsine, leurosine.[21] Alkaloids present in different organs can be summarized below.

Table 2: It explains the name of Alkaloids present in different organs of the plant.

Plant organ	Name of Alkaloids present.
Leaf	Catharanthine, Vindoline, Vindolidine, Vindolicine, Vindolinine, ibogaine, yohimbine, raubasine, Vinblastine, Vincristine, Leurosine, Lochnerine.
Stem	Leurosine, Lochnerine, Catharanthine, Vindoline.
Root	Ajmalacine, Serpentine, Catharanthine, Vindoline, Leurosine, Lochnerine, Reserpine, Alstonine, Tabersonine, Horhammericine,Lochnericine, echitovenine.[22]
Flower	Catharanthine, Vindoline, Leurosine, Lochnerine, Tricin (Flavones).
Seeds	Vingramine, Methylvingramine.[23]

Among this vinca alkaloids present in Catheranthusare bulky molecule with closely related structure, containing both an indole nucleus (catharanthine portion) and a dihydroindole nucleus (vindoline portion) connected by a carbon-carbon ring.[24] Naturally occurring Vincristine and vinblastine, semi -synthetic Vindesine and Vinorelbineare Vinca alkaloids.[25] extracted from periwinkle plant are effective against different types of cancers.

Pharmacologicalactivities

1. Anti-oxidant activity

Reactive oxygen species are the harmful byproducts created in our body in normal aerobic respiration and other metabolic activities. Antioxidants are found to be effective against these harmful free radicals.[26] *C.roseus* produce phenolic compounds which is an effective anti-oxidant. Oxygen radical absorbing capacity (ORAC) of *C. roseus*in 2011, Rassoland colloguesdemonstrated that C.roseus is a viable source of natural oxidants which can be applied in food and nutraceuticalindustry. The anti-oxidantproperties of two varieties of *C.roseus* that is pink flowered and *C.alba* were compared and was found that *C.roseus* possess more antioxidant activity than that of *C. alba*.[27]

2. Anti-diarrheal activity

The anti-diarrheal activity of the plant ethanolic leaf extract was tested in the wistar rats with castor oil as an experimental diarrhea inducing agent in addition to the pretreatment of the extract. Loperamide and atropine sulphate was used as the standard drugs. Theanti-diarrheal effect of ethanolic extracts *C. roseus* showed the dose dependent inhibition of the castor oil induced diarrhea at the doses of 200 and 500 mg/kg.[28]

3. Anti-diabetic activity

The ethanolic extracts of the leaves and flower of *C. roseus* showed a dose dependent lowering of blood sugar comparable to the standard drug glibenclamide. The Hypo glycemic effect is due to the increased glucose utilization in the liver.[29] The hypoglycemic activity of alkaloids isolated from *C.roseus* have been studied pharmacologically and a natural remedy derived from the plant has been marketed under the proprietary name Vinculin® as a treatment for diabetes.[30]

Alcoholic whole plant extracts at high dose (500 mg/kg) exhibited significant antihyperglycemicactivity without acute toxicity. The extract effectively reverses the changes in the blood sugar level and the beta-cell population. The exact phytoconstituents responsible for the anti-diabetic effect are not known yet.[31]

4. Anti-microbial activity

The phytochemical and antimicrobial studies made on C. roseus have shown that it has very important antimicrobial components alkaloids, flavonoids, steroids, phenolics, tannins and saponins. The methnol, ethanol, acetone and chloroform extracts of these plants have shown antibacterial activity against commonhuman pathogens Escherichia coli, Vibrio cholerae, Styphylococcusaureus and Streptococcus faecalis. The discovery of a potent remedy from plant origin will be a great advancement in bacterial infection therapies as most of the bacterial pathogens were developing resistance against many of the available anti-microbial drugs.[32] The antimicrobial activities of plant extracts may reside in a variety of different components, including aldehydes and phenolic.[33]

5. Anti-Cancer activity

C.roseus produces Vinca alkaloids which are well known for their anti-cancer properties. Some of the alkaloids are vinblastine, vincristine, vinorelbineand vindesine.[34] Following table shows the alkaloid name, the branded drug name and its therapeutic uses.

Table 3: It shows the name of Vinca alkaloids, branded drug names and its therapeutic uses.

Vinca alkaloid	Related drug	Therapeutic uses
Vincblastine	Velban	Hodgkins disease, testicular germ cell cancer
Vincristine	Oncovin[35]	Leukemia, lymphomas
Vinorelbine[36]	Navelbine	Solid tumors, lymphomas, lung cancer
Vindesine[37]	Eldisine[38]	Acute lymphocytic leukemia

Anti-cancer drugs derived from *C.Roseus* act us inhibitors of tubulin by binding to α/β- –tubulin. This prevents its association in to microtubules which provide cells with both the structure and flexibility they need to divide and replicate.[39,40] That is microtubules are the building block of protein and is vital to the proper functioning of the mitotic spindle in mitosis i.e., cell division. Vinca alkaloids known as mitotic spindle poisons as they inhibit further assembly of the spindle forms from microtubules, there by inhibiting mitosis in cell cycle.[41] Vinca alkaloids thus successfully prevent cancer cells from dividing. Different Vinca alkaloids have their own unique properties. Among this Vincristine's inhibition of microtubule formation is especially powerful. Overall, Vinca alkaloids are in the second most-used class of cancer drugs. Though, it will remain on top among the fundamental cancer remedies. Research for new Vinca alkaloid applications is ongoing.[42] Currently Niosomes are used as drug carriers for vincristine and its toxicity was reduced after encapsulation and anti-cancer activity was improved.[43] For many years scientists have involved in the process to synthesize new derivatives of vinblastine and vincristine. Modification in vindoline skeleton or catharanthine moiety produced a number of new selective, less toxic antitumor agents.[44]

5. Anthelminthic activity

C.roseus was found to be used from the traditional period as an anthelminthic agent. The anthelminthic property of *C.roseus* has been tested by using Pherithemaposthuma as an experimental model and with Piperazine citrate as the standard reference. Then theethanolic extract of the concentration of 250 mg/ml was found to show the significant anthelminthic activity. This analysisreinforced the ethnomedical claims of *C.roseus* as an anthelminthic plant.[45]

6. Anti-ulcer activity

The plant leaves proved for anti-ulcer activity against experimentally induced gastric damage in rats.[46] Vincamine and Vindoline alkaloids of the plant showed anti-ulcer property. The alkaloid vincamine, present in the plant leaves shows cerebrovasodilatory and neuroprotective activity.[47]

7. Hypotensive activity

Extract of leaves of the plant shows significant change in hypotensive. The leaves have been known to contain many useful alkaloids among other pharmacologically active compounds. Significant hypotensive activity of the leaf extracts (hydroalcoholic or dichloromethane-methanol) have been reported in laboratory animals.[48]

8. Hypolipidimic effect

Significant anti-atherosclerotic activity of *C.roseus*was observed in a study with reduction in the serum levels of total cholesterol, lipid profiles, triglycerides and histology of aorta, liver and kidney with the leaf juice of *C. roseus*.[49]

9. Memory enhancement activity

Vinpocetine the most intriguing dietary supplement madefrom the alkaloid called vincamine. It has been reported to have a variety of actions to improve brain function and memory, particularly beneficial in Alzheimer's disease. Vinpocetine has been well tolerated at doses up to 60 mg/d in clinical trials of dementia and stroke and no significant adverse events were observed.[50] Vinpocetine should not be combined with any blood thinning agents such as warfarin, aspirin as well as some dietary supplements like ginkgo, vitamin E and garlic.[51]

10. Wound-Healing activity

When wounded Rats treated withethanolic extract of the *C.roseus*shows high rate of wound contraction. This is due to increased tensile strength and hydroxyproline content of the granulation tissues. It supports the uses of *C. roseus* in the management of wound healing.[50]

Toxicity and Side effects

*C.roseus*is not recommended for oral administration becauseit may worsen the side effects including psychological influences. The advised route for *C.roseus* and its derivatives are intravenous. Vinca alkaloids have been applied clinically since the end of the 1950s as major drugs in the treatment of Hodgkins disease, testicular germ cell cancer, lymphomas, Solid tumors, lung cancer and acute lymphocytic leukemia etc.[52] In spite of their extraordinary benefits, all of the *C. roseus* alkaloids have neurotoxic activity, particularly vincristine, affecting neurotransmission.[53] Vincristine and vinblastine are highly toxic antimitotic, blocking mitosis in metaphase after binding to the microtubules.[54] Moreover, many side effects have been reported for these drugs comprising abdominal pains, constipation, nausea/vomiting, ulcerations of the mouth, celldestruction, kidney damage, pulmonary fibrosis, urinary retention, amenorrhea, hypotension and hypertension.[53,55&56] Hence the dosage and administration must be cautiouslymeasured to reduce side-effects.

CONCLUSION

*Catharanthusroseus*is a rich source of lifesaving drugs especially Vinca alkaloids which are widely used to produce anti-cancer drugs. They continue to be an important therapeutic aid in future due to the proximity of vast phytochemicals present. Several researches are going on recently to decrease the toxicity of Vinca alkaloids, increase the yield of alkaloids in the plant by developing new varieties and to improve its therapeutic effects.[57] Some successful results are also derived. For instance vincristine encapsulated nanoparticles have promising future in drug delivery as its toxicity was reduced and anti-cancer activity was improved after encapsulation.[43]

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